and the more adversely located carcinomas of the common duct. These more favorable features have resulted in lower operative death rates, only 12.4% in a collected series of 370 cases of pancreaticoduodenectomy for ampullary carcinoma.[2] To this mortality must be added the frequent morbidity of pancreatic fistulas, which occurred in 18.5% of one series. Results of surgical treatment of ampullary carcinoma, however, seem adequately satisfactory to justify this operative morbidity and mortality. In the largest reported experience, that of Warren and co-workers, 37.5% of 48 surgically treated patients survived for more than five years, and in a collected group of 111 patients, 27% survived five years.[1,2,4,5] It should be emphasized, however, that many of these tumors are indolent and five-year survival does not necessarily imply cure. Two of the eight five-year survivals of Monge and associates later had recurrence of their cancer.[4]

Palliative Treatment. The most definitive palliative procedure for unresectable ampullary carcinoma is bypass, which usually is accomplished by cholecystoduodenostomy. Radiation therapy has no established role. Experience with chemotherapy has been meager. We have observed a single objective response to 5-fluorouracil, and although we presume ampullary carcinomas probably respond to this agent with approximately equal frequency and duration as other gastrointestinal adenocarcinomas, we have insufficient data to prove this presumption. The same measures of symptomatic and supportive care that are discussed in the chapter on pancreatic carcinoma are applicable to the patient with ampullary cancer.

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XXIV-7. *Exocrine Pancreas*

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Translations of Josephius Flavius, vividly describing the terminal illness of King Herod of Judea, make it seem likely that the evil murderer of the children of Bethlehem died of carcinoma of the pancreas.[9] One would hope that affliction with this neoplasm is not a manifestation of divine judgment, since the incidence of pancreatic cancer seems to be steadily increasing in our society. It now ranks fourth as a cause of cancer deaths, exceeded only by cancer of the lung, the large bowel, and the breast.

Incidence. It is estimated that 19,000 Americans will develop pancreatic carcinoma in 1973, and that essentially the same number will die of this neoplasm.[1] These figures undoubtedly are substantially underestimated, since in many such patients the condition is first diagnosed by biopsy of metastasis, and the primary pancreatic site is never definitely established unless an autopsy is performed. It is perhaps surprising to realize that deaths from cancer of the pancreas now exceed those from cancer of the stomach and almost double those from cancer of the rectum. The rate of increase in occurrence of reported cases of carcinoma of the pancreas in recent years

Exhibit E

has been striking, indeed, second only to that of lung cancer. It is problematic, however, how much of this reported increase might be due to improved case finding.

Etiology. The cause of pancreatic carcinoma remains unknown, and indeed there is little circumstantial evidence from either experimental animals or epidemiologic studies on which to base even a tentative hypothesis.

The possible etiologic factors most often cited are chronic pancreatitis, diabetes mellitus, and alcoholism. Essentially all of the evidence supporting these factors as etiologic is retrospective in nature and based on reviews of case histories. The many sources of error in any such studies of the association of diseases are compounded by the fact that both diabetes mellitus and the pathologic changes of chronic pancreatitis may be produced by carcinoma of the pancreas. Prospective controlled studies on large populations must produce confirmation before any of these coincident illnesses can be accorded a causative role.

Pathology. In Table XXIV-7-1 the cell-specific types of carcinoma of the pancreas are classified with their proportionate frequency of occurrence. By analyzing individual and collective series, it can be concluded that about 75% of pancreatic carcinomas either arise in or involve the head of the gland, and the remainder are confined to the body or tail. In surgical series preponderance of lesions primary to the head is even greater, since clinically many tumors of the body and tail are first diagnosed by the detection of metastasis, and laparotomy is not performed.

Grossly, the neoplasm, when diagnosed surgically, is usually relatively small, and almost all tumors are solid and scirrhous. They are firm to palpation and surrounded by a zone of pancreatitis, which frequently accounts for the bulk of the mass. In many instances, the tumor itself accounts for less than one-third of the gross abnormality. Surrounding pancreatitis accounts for much of the difficulty in surgical diagnosis. Many carcinomas are interpreted as pancreatitis even after deep biopsy, and many cases of pancreatitis have been grossly diagnosed as carcinomas. Occasionally, pancreatitis distal to a carcinoma obstructing the duct may give rise to a pseudocyst that is the patient's presenting clinical problem. Histologically, pancreatic carcinomas most commonly show ductal or acinar architecture, but a high degree of anaplasia may defy such designation. Rarely, squamous cell histology is observed, probably originating from metaplasia of the major ducts. Most neoplasms are relatively undifferentiated, with about two-thirds graded 3 or 4 by Broder's classification (grade 1, well differentiated, to grade 4, highly undifferentiated).

Extension of the tumor in the head of the gland produces invasion of the common duct or compression of the uninvolved duct against the duodenum. In either case, obstruction results with jaundice and dilatation of the bile ducts and gallbladder. Further extension of carcinoma of the head of the pancreas may involve the adjacent duodenum, stomach, colon, kidney, or vena cava with resultant hemorrhage or obstruction. Carcinomas of the body of the pancreas quickly involve the superior mesenteric vessels or portal vein rendering the tumor inoperable. Tumors primary to the tail may invade or compress the portal or splenic vessels, producing portal hypertension with splenomegaly and esophageal or gastric varices. Either the pancreatic cancer itself or hepatic metastasis may involve the hepatic vein, producing thrombosis and the clinical manifestations of the Budd-Chiari syndrome. Neural involvement can be demonstrated histologically for tumors of all sizes, accounting for the significant pain these patients experience.

Metastasis from carcinoma of the pan-

TABLE XXIV-7-1. Cancers primary to the exocrine pancreas

Adenocarcinomas	
Ductal cell	82%
Acinar cell	13%
Anaplastic	5%
Cystadenocarcinomas	rare
Adenoacanthomas	rare
Squamous cell carcinomas	rare
Sarcomas	rare

TABLE XXIV-7-2. The natural history of pancreatic carcinoma; survival from histologic proof of unresectable cancer

	No. of patients	*Survival (months)*	
		Mean	*Median*
A. According to sex			
Male	94	6.3	3.5
Female	51	5.1	4.5
B. According to age			
20–39	4	3.8	3.5
40–59	56	5.5	4.0
60–79	84	6.1	3.5
C. Location of primary			
Head	84	6.9	4.0
Body	62	4.8	3.0
Tail	14	3.4	2.5
D. Grade of malignancy (Broders)			
1 and 2	51	8.8	5.5
3 and 4	94	4.2	3.0
E. Duration of symptoms (months)			
0–6	84	4.7	3.5
Over 6	61	7.5	4.5
F. Extent of disease at diagnosis			
Regional only	67	8.8	6.0
Distant intra-abdominal	27	4.2	3.0
Hepatic	50	3.1	2.5
Extra-abdominal	8	2.5	2.0

creas is frequent and usually occurs early in the course of the disease. Regional lymph nodes and the liver are the most common sites and are involved at about an equal rate. Peritoneum, lungs, and pleura are also frequently involved with further progression of the disease. Adrenals, bone, and spleen are among the more common sites for advanced metastatic disease, but literally any site may be involved.

Death probably results most frequently from hepatic failure secondary to obstruction or hepatic replacement by metastasis.

From the standpoint of natural history, pancreatic carcinoma is quite virulent. Among 145 patients with histologically proved pancreatic adenocarcinoma whom we have followed, the median survival from onset of symptoms was 10.5 months (mean 12.8 months) and from proof of unresectable carcinoma, 3.5 months (mean 5.9 months).[11] It is demonstrated in Table XXIV-7-2 that survival was unrelated to sex. Survival among patients with tumors of the body and tail was lower than it was among those with tumors of the head, perhaps related to earlier diagnosis of tumors in this latter area. As might be predicted, survival was less for the more undifferentiated tumors, for those with a shorter clinical history, and for those with more distant metastatic disease at the time of initial diagnosis.

Clinical Features.[2,8] Cancer of the pancreas has had a preference for the male over the female in essentially all reports ranging from 1.5:1 to 3:1. All age groups including early childhood have been afflicted, but the incidence increases steadily with advancing age, and these neoplasms become most prevalent in the seventh decade. The mean age at diagnosis in a number of reports is in the vicinity of 57 years.

Symptoms. **Pain.** Pain is the presenting and predominant symptom in the great majority of patients with carcinoma of the pancreas, regardless of location of the primary lesion. This will characteristically be insidious in onset and gradually progressive.